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10/523,756	06/29/2006	Derek Hart	18638	2472

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EXAMINER	
JUEDES, AMY E	

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1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,756	HART, DEREK	
	Examiner	Art Unit	
	AMY E. JUEDES	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,10-12,14-16,18-22,25-30 and 33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,10-12,14-16,18-22,25-30 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 2/17/09, are acknowledged.
Claims 6-7, 9, 13, 17, 23-24, and 31-32 have been cancelled.
Claims 1, 8, 10, 15-16, 18, 20, and 25-27 have been amended.
Claim 33 has been added.
Claims 1-5, 8, 10-12, 14-16, 18-22, 25-30, and 33 are pending and are under examination.

2. The objection to claim 15 for being an improper multiple dependent claim is withdrawn in view of Applicant's amendment. Thus, claim 15 is no longer withdrawn from consideration and is being included in the examination.

3. The objection to claims 13 and 24 and the rejections of claims 31-32 under 35 U.S.C. 101 and 112 are moot, in view of the cancellation of the claims.

4. The rejection of the claims under 35 U.S.C. 112 second paragraph and under 112 first paragraph for lack of written description are withdrawn in view of Applicant's amendment to the claims.

5. The rejection of the claims under 35 U.S.C. 102 as being anticipated by WO 99/24078 is withdrawn in view of Applicant's amendment to the claims. WO 99/24078 does not teach an antibody which binds to CMRF-44.

6. The rejection of the claims under 35 U.S.C. 112 first paragraph for lack of enablement is withdrawn in part, in view of Applicant's amendment to the claims to remove the term modulating, and to limit the claims to methods employing an antibody binding to CMRF-44. However, the claims stand rejected under 112 first paragraph for the recitation of a method of "preventing" the immuno-activity of an APC (see below).

7. In view of Applicant's amendment to the claims, the previous rejection of the claims for obviousness type double patenting is withdrawn. However, Applicant's arguments relevant to the new grounds of rejection will be addressed below.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5, 8, 10-12, 14, 16, and18-22 stand rejected, and claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting or downregulating the immuno-activity of an APC comprising contacting said APC with an antibody or fragment thereof specific for CMRF-44, and a method for inhibiting or downregulating an immune response in a subject comprising administering to the subject an antibody or fragment thereof specific for CMRF-44,

does not reasonably provide enablement for a method for preventing the immuno-activity of an APC comprising contacting said APC with an antibody or fragment thereof specific for CMRF-44 and a method for preventing an immune response in a subject comprising administering an antibody or fragment thereof specific for CMRF-44.

As set forth previously, The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, in re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information

needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable.

The specification provides insufficient guidance to enable claims drawn to the method as broadly claimed. The claims encompass not only downregulating the activities of a cell, but preventing said activities. This encompasses completely preventing any functional activity of the cells using an antibody. While it may be possible to downregulate or inhibit the activities of said cells by inducing cell lysis with an antibody (for example, an antibody conjugated to a toxin), a complete prevention would require lysing every cell. Furthermore, the instant specification only discloses a single example of using an antibody specific for CMRF-44 to induce lysis of APCS, hence downregulating (but not "preventing") the immunoactivity of said APC. The specification further demonstrates that APC populations treated with said antibody have a reduced ability to stimulate T lymphocytes. However, this is not commensurate in scope with the instant claims .

Applicant's arguments filed 2/17/09 have been fully considered, but they are not persuasive.

Applicant argues that the amendment to the claims obviates the rejection.

However, the claims still recite that the method is a method for "preventing" the immuno-activity of an APC. Additionally, claim 20 has been amended to recite that the method is a method for "preventing" an immune response in a subject. As noted above, the term "prevention" encompasses a complete prevention. Thus, the claims encompass a method of completely preventing all immune-activities of APCS or completely preventing an immune response in a subject using an antibody specific for CMFR-44. As noted above, while it may be possible to reduce or inhibit the immuno-activities of an APC or an immune response with an antibody, for example by inducing cells lysis, a complete prevention would require lysing every cell which would be extremely unpredictable. In fact, as noted above, the examples in the specification demonstrate that while CMRF-44 antibodies can downregulate or inhibit the ability of APC populations to stimulate T cells in vitro (i.e. an immuno-activity of an APC), they do not "prevent' the ability of the APC to stimulate T cells, since CMRF-44 treated APC populations still stimulate some T cell proliferation (see Fig. 8, for example). Thus, it would require undue experimentation to "prevent' the immuno-activity of an APC or prevent an immune response using a CMFR44 specific antibody, as claimed.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-5, 8, 10-12, 16, and 18-19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Koppi et al., 2001, Immunol. and Cell Biol.

As set forth previously, Koppi et al. teach a method of inducing dendritic cell lysis (i.e. downregulating the immuno-activity of an antigen presenting cell) comprising contacting human dendritic cells with a monoclonal antibody specific for CMRF-44. Koppi et al. teach that the lysed dendritic cells are CD11c positive (i.e. myeloid DCs).

Applicant's arguments filed 2/17/09 have been fully considered, but they are not persuasive.

Applicant argues that the PBMC cells of Koppi et al. were labeled with CMFR-44 antibody and incubated with complement. Thus, Applicant concludes that the death of the dendritic cells is caused by the complement and not by the antibody.

Incubation with complement is well known to result in the cell lysis of the those cells bound by the antibody (i.e. the antibody mediates the complement induced cell lysis). In fact, the instant specification on pages 20-21 teaches that complement mediated lysis is particularly suited to the immuno-therapeutic applications wherein the destruction of specific cells with an antibody is desired. Additionally, the instant specification on page 38 and 43 teaches specific examples in which CMRF-44 antibody treated PBMC are incubated with complement as a means of inducing APC lysis. Thus, the instant claims clearly encompass methods wherein cell lysis in induced by a CMRF-44 antibody in combination with complement.

Applicant further argues that Koppi et al. teach that CMRF-44 antibody may be suitable for targeting dendritic cells instead of lymphocytes, and that thus, Koppi et al. do not disclose that CMRF-44 antibody by itself had an immunomodulatory effect on dendritic cells.

Koppi et al. teach the exact method of the instant claims. Killing and lysis of dendritic cells (i.e. an APC) in a PBMC population as taught by Koppi et al. would inherently result in the downregulation of the activity of the dendritic cells, as recited in the instant claims. Lymphocytes are not required in the method of the instant claims, and the teachings of Koppi et al. regarding the ability of the CMRF-44 antibodies to target lymphocytes are not relevant.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8, 10-12, 14, 16, 18-22, and 25-30 stand rejected, and claim 15 is rejected, under 35 U.S.C. 103(a) as being unpatentable over WO 99/24078, in view of U.S. Patent 5,876,917, as evidenced by Flavell et al., 1998, Cancer Research.

As set forth previously, WO 99/24078 teaches a method of depleting antigen presenting cells (i.e. a method of downregulating the immuno-activity of an antigen presenting cell) comprising contacting the antigen presenting cell with an antibody specific for an antigen expressed by APCs (see page 3 and 20-21 in particular). WO 99/24078 teaches that the depleted antigen presenting cells can be dendritic cells, B cells, or macrophages (see page 3 in particular). WO 99/24078 teaches that the antigen presenting cells may be depleted using an antibody immunotoxin that binds to various antigen presenting cell markers (see page 10-11 in particular). Additionally, WO 99/24078 teaches depleting human cells, and that the method results in the killing of the APC (i.e. cell lysis, see page 3 and 10, in particular). WO 99/24078 also teaches monoclonal antibodies (see page 12 in particular). WO 99/24078 also teaches depleting the APCs in vivo (i.e. modulating an immune response in a subject) to treat graft versus host disease resulting from an alloimmune attack on host tissues initiated by host-APCs. (see page 9, 20 and 22 in particular). WO 99/24048 teaches treating said graft versus host disease (i.e. a method of down regulating the immunoactivity of a graft or treating a condition characterized by the inappropriate immunoactivity of a graft) by administering the antibodies to a subject (see page 20 and 22 in particular). WO 99/24078 also teaches that the antibodies can be administered concurrent with allogenic bone marrow transplantation (i.e. the administration of the antibodies results in the "contact" of the bone marrow graft with the antibodies, see page 20 in particular).

WO 99/24078 does not teach an antibody specific for CMRF-44.

The '255 patent teaches an antibody specific for CMRF-44 which is expressed by activated antigen presenting cells, including dendritic cells (see column 3 in particular). The '255 patent further teaches that CMRF-44 is a marker that can be used to specifically identify allostimulatory populations of antigen presenting cells.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the therapeutic method of treating graft versus host disease by administering an antibody specific for an antigen presenting dendritic cell, as taught by WO 99/24078, using the CMRF-44 antibody taught by the '255 patent. The ordinary artisan would have been motivated to do so, and have a reasonable expectation of success, since WO 99/24078 teaches that antibody depletion of antigen presenting cells that initiate an alloimmune attack is useful for treating graft versus host disease, and the '255 patent teaches that antibodies specific for CMRF-44 identify activated, allostimulatory populations of antigen presenting cells. Additionally, it would have been obvious to use the CMRF-44 antibody of the '255 patent conjugated to an immunotoxin as a means to deplete APCs, as taught by WO 99/24078. As evidenced by Flavell et al., administration of immunotoxin antibodies results in lysis of target cells by a variety of mechanisms, including antibody-dependent cellular cytotoxicity.

Applicant's arguments filed 2/17/09 have been fully considered, but they are not persuasive.

Applicant argues that as evidenced by Hock et al., the mere knowledge of the existence of an APC-binding antibody would give the skilled artisan no expectation that such antibody would be useful for modulating the function of the cells that the antibody bound to.

The references cited by Applicant demonstrate that not all dendritic cell specific antibodies modulate the activities of the dendritic cells. However, the references cited in the 103 rejection make obvious a method of depleting dendritic cells in vivo using an antibody conjugated to a toxic component (i.e. an immunotoxin). It would have been obvious to use CMRF-44 as the dendritic cell specific antibody, since the '255 patent teaches that it is a expressed by allostimulatory populations of dendritic cells. Furthermore, the ordinary artisan would have had a reasonable expectation that linking the antibody to a toxin (as taught by WO 99/24078) would induce lysis of CMRF-44 expressing cells in vivo, thus "downregulating" the immuno-activities of the cells. Therefore, whether or not a CMFR-44 antibody by itself modulates the activities of dendritic cells by other mechanisms (for example inducing cell signaling) is not relevant. The ordinary artisan would easily recognize that induction of cells lysis by a toxin conjugated CMRF-44 antibody, as made obvious by the cited references, would result in the inhibition of the activities of the lysed cells.

13. The following are new grounds of rejection necessitated by Applicant's amendment.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-30 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 25-26 recite the limitation "said APC" in line 5, and claims 27 and 30 recite the limitation "said APC" in line 6. There is insufficient antecedent basis for this limitation in the claims.

15. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable Faustman et al., 1984, in view of U.S. patent 5,876,917 (of record).

Faustman et al. teach a method of inhibiting graft rejection (i.e. an unwanted "immuno-activity" of a graft), said method comprising contacting the graft with an antibody specific for dendritic cells in vitro prior to transplantation. Faustman et al. also teach inducing lysis of the antibody bound dendritic cells with complement (i.e. under conditions sufficient to induce cell lysis) before transplantation. Faustman et al. teach that the depletion of dendritic cells in the graft prior to transplantation is effective in inhibiting graft rejection, since said dendritic cells initiate the rejection of the graft (see page 3867 in particular).

Faustman et al. do not teach an antibody specific for CMRF-44.

The ‘255 patent teaches an antibody specific for CMRF-44 which is expressed by dendritic cells (see column 3 in particular). The ‘255 patent further teaches that CMRF-44 is expressed by allostimulatory populations of dendritic cells.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to perform the method of inhibiting graft rejection employing a dendritic cell specific antibody, as taught by Faustman et al, using the CMRF-44 antibody taught by the '255 patent. The ordinary artisan would have been motivated to do so, and have a reasonable expectation of success, since Faustman et al. teach that antibody depletion of dendritic cells that initiate an alloimmune attack is useful for inhibiting graft rejection, and the ‘255 patent teaches that antibodies specific for CMRF-44 bind to allostimulatory populations of dendritic cells.

16. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5, 8, 10-12, 14-16, 18-22, and 25-30 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 9 of copending Application No. 10/524,716, in view of U.S. Patent 5,876,917 and WO 99/24078 (both of record).

Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 9 of the '716 application is drawn to a method of inhibiting an immune response in a subject comprising administering to a subject an antibody which binds to a dendritic cell surface activation molecule under conditions to induce cell lysis. It would have been obvious to perform the method to inhibit graft versus host disease after bone marrow transplantation as the immune response, since WO 99/24078 teaches that depletion of allostimulatory dendritic cells with antibodies specific for dendritic cell surface molecules is effective for inhibiting GVHD. Additionally, it would have been obvious to use the CMRF-44 antibody of the '917 patent in said method, since the '917 patent teaches that CMRF-44 is an activation molecule expressed by allostimulatory dendritic cells.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's statement that the provisional obviousness type double patenting rejection can be overcome with a terminal disclaimer is acknowledged.

17. No claim is allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE

MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, whose telephone number is 571-272-4471. The examiner can normally be reached on 7am to 3:30pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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